



RESEARCH ARTICLE

Evaluation of Pineal Gland in Patients with Schizophrenia

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ABSTRACT

Recent advancements in neuroimaging techniques have facilitated the identification of numerous structural brain alterations associated with schizophrenia, potentially serving as valuable biomarkers. This study aimed to explore the volumetric changes in the pineal gland correlated with schizophrenia symptoms, employing standard brain segmentation methodologies. The study encompassed 135 participants, comprising 82 controls and 53 patients, all of whom provided voluntary consent. Magnetic resonance imaging (MRI) of the brain was conducted using the magnetization prepared rapid acquisition protocol, and the acquired images were processed through BrainSuite software. Statistical analysis was done to determine the significance of volumetric differences in the pineal gland between patients and controls. In addition, it assessed any correlations with demographic variables, such as age and sex. The control group's mean age was 29.28 ± 6.03 , while the patient group was 31.32 ± 6.44 . No significant differences were observed between the groups in terms of sex or age distribution, with $P = 0.583$ and 0.064 , respectively. The average pineal gland volume in patients with schizophrenia was $48.82 \pm 20.39 \text{ cm}^3$, markedly lower than the $64.23 \pm 26.51 \text{ cm}^3$ observed in controls. The findings indicate that individuals with schizophrenia possess smaller pineal glands compared to the general population. It is concluded that MRI is a viable tool for assessing structural brain changes linked to schizophrenia, and the pineal gland may play a contributory role in the disease's pathogenesis.

Keywords: Schizophrenia, brain suite, volumetric changes, pineal gland, magnetic resonance images

INTRODUCTION

Schizophrenia is a chronic psychotic illness characterized by myriads of positive and negative psychotic symptoms.^[1] It is often progressive and disabling disease that is associated with great social stigma.^[2] Moreover, despite of the huge advances neuroscience and psychiatry that culminate in major developments in the diagnosis and management of all psychiatric illnesses, the schizophrenia remains of unknown and doubtful pathophysiological mechanism and natural history.^[3]

Since very early on when Schizophrenia was first reported in 1908, it was hypothesized to be associated with brain structural changes.^[4] This waited for a very long period of time till the recent tremendous advances in structural and functional neuroimaging techniques have opened the door for the researchers to study the detailed structural and functional alterations in the brain that are found in patients with schizophrenia.

Many studies addressed the issue of structural brain changes in schizophrenia. Elfaki *et al.* reported that patients with schizophrenia have significantly smaller brains than their

matching controls and they have bigger mean volume of white matter and larger volume of ventricular system.^[4] Interestingly, these changes were found to affect not only patients with schizophrenia but also their first-degree family members when compared to controls with no family history of schizophrenia.^[1]

Recent research focuses more on melatonin's potential role in schizophrenia. Melatonin is a hormone, similar to indole, produced by the pineal gland. It is crucial for regulating our sleep-wake cycle. In addition, it acts as a strong antioxidant, helping to remove harmful substances. It also

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plays a role in the immune system and in fighting cancer.^[2] People with schizophrenia often experience sleep and daily rhythm problems. Since melatonin helps control these cycles and sleep patterns, it might be involved in the development of schizophrenia. Furthermore, serotonin is another chemical produced by the pineal gland. It is important for mood regulation. Many mental health medications target serotonin.

The pineal gland is a small pinecone shaped gland located in the epithalamus weighs about 10 g and measures about 8x4 mm in normal adults.^[3,4] Research into the volume changes of the pineal gland in schizophrenic patients is relatively limited, and the findings have been mixed. Some studies have suggested that there may be volume changes in the pineal gland in schizophrenia, but the results are not consistent. In the current study is addressing the issue of the volumetric changes that occur in the pineal gland of patients with schizophrenia comparing them with normal controls using standard conventional brain segmentation techniques.

PATIENTS AND METHODS

This study involved 82 control subjects (47 males and 35 females) and 53 patients (27 males and 26 females), totaling 155 volunteers. It received approval from the Ethical Committee of Gezira University, Sudan. Informed consent was obtained from all participants or their relatives in the case of patients.

The patient group consisted of adult Sudanese individuals clinically diagnosed with schizophrenia, all of whom met the ICD/10 criteria and were under regular antipsychotic treatment. These patients were recruited from Professor Abdelaal Alidresi Psychiatric Hospital, Tigani Almahi Psychiatric Hospital, and various private psychiatric clinics across Sudan.

The control group comprised Sudanese volunteers without any psychiatric disorders or medication history, carefully matched with the patient group in terms of gender and age.

Both groups were screened to exclude individuals with a history of head trauma, drug abuse, or central neurological disorders.

Magnetic Resonance Imaging (MRI) Acquisition

Structural MRI scans were performed on both patients and controls at the Department of Radiology, National Ribat University. The equipment used was a SIEMENS 1.5 Tesla Magnetom Avanto Vision System. For imaging, we employed a three-dimensional T1-weighted sequence using magnetization prepared rapid acquisition (MP-RA), which is known for its efficient grey/white matter contrast and brief acquisition time. The settings were as follows: Slice thickness of 1.0 mm, field of view of 250 mm (read) by 192 mm (phase), repetition time of 1657 ms, echo time of 2.95 ms, bandwidth of 180 Hz/pixel, flip angle of 15°, ECHO spacing of 7.5 ms, phase resolution at 100%, slice resolution at 50%, and a total acquisition time of 5 min and 18 s. Images were captured in the coronal plane.

This T1-weighted imaging sequence is routinely included in clinical protocols for both qualitative and quantitative brain analysis, particularly in patients with epilepsy.

Automatic Segmentation of the MRI

The DICOM images from the study participants were analyzed using BrainSuite software, with the analysts blinded to the clinical data. These images were directly uploaded into BrainSuite, a comprehensive suite of tools designed for neuroimaging data analysis. BrainSuite facilitates the quantification of the human brain's functional, connective, and structural attributes through a series of advanced algorithms. Originally developed to produce surface representations of the cerebral cortex, BrainSuite has evolved to automatically generate models of most macroscopically visible brain structures from any suitable T1-weighted MRI scan. The volume of the pineal gland was automatically calculated by BrainSuite. Following a quality control process, these measurements were directly utilized in statistical analyses.

RESULTS

We included 135 subjects (82 controls and 53 schizophrenic patients) in our study. In the control group, there were 47 (57.3%) males and 35 (42.7%) females while there were 27 (50.9%) male patients and 26 (49.1%) female patients in the schizophrenic patients' group. There was no difference between our groups regarding sex distribution ($P = 0.583$). In the control group, the mean age was 29.28 ± 6.03 and in the schizophrenic, in the patients group, the mean age was 31.32 ± 6.44 . There was no difference between our groups regarding age ($P = 0.064$).

In schizophrenic group, 16 (30.2%) patients were using typical antipsychotic and 37 (69.8%) patients were using atypical antipsychotic.

The comparison between control and patients with schizophrenia groups regarding the mean volume of the pineal gland showed significant difference between the groups. The mean volume of the pineal gland of patients with schizophrenia ($64.23 \text{ cm}^3 \pm 26.51$) was lower than that of the controls ($64.23 \text{ cm}^3 \pm 26.51$). However, there was no significant difference for the mean volume of the pineal gland between sex ($P = 0.480$).

Pineal gland volume (mm ³)		
Case	n	Mean (cm ³) \pm std deviation
Controls		
Male	47	64.89 \pm 27.90
Female	35	63.34 \pm 24.90
Total	82	64.23 \pm 26.51
Patients with schizophrenia		
Male	27	51.06 \pm 23.40
Female	26	46.49 \pm 16.84
Total	53	48.82 \pm 20.39

DISCUSSION

This structural MRI-based study is comparing the volume of the pineal gland between 82 healthy controls and 53 patients with schizophrenia. Our major findings in this study are that

patients with schizophrenia have a statistically significant smaller total intracranial volume and pineal gland volume. This may suggest a possible pathogenetic involvement of the pineal gland in schizophrenia and other psychotic spectrum disorder.

These findings are supporting the findings of Findikli *et al.* who reported that patients with schizophrenia have a significantly smaller pineal gland not only when compared to healthy controls but also in comparison to patients of unipolar depression and bipolar mood disorder.^[5] Similar results were obtained by Bersani *et al.*^[6] In a study by Rajarethinam *et al.*, they reported contradicting results that there is no volumetric difference between patients with schizophrenia and controls.^[7] Despite their very large sample size in this study but they did their measurements using a locally developed software and there was no information about the duration of illness or the medications used by their patients.

Pineal gland changes were also reported in many studies for example pineal gland calcification is well known to occur in patients with schizophrenia.^[8]

When compared with the study by Takahashi *et al.* (2019), the pineal volume of the chronic patients with schizophrenia is similar to the data in our study when compared to healthy controls.^[9]

Changes in the pineal gland observed in patients with schizophrenia can be understood through the lens of either the neurodevelopmental or neurodegenerative theories of schizophrenia pathogenesis. It is proposed that the development of certain brain regions, including the pineal gland, may be delayed early in life, while neurodegenerative processes could alter the molecular structure of the pineal gland, leading to a reduction in its size.^[6] This hypothesis is bolstered by studies reporting the presence of pineal calcifications in patients with schizophrenia.^[10]

In a systematic review and meta-analysis study by Bastos *et al.* for Pineal gland and schizophrenia, imaging studies showed that enlarged calcifications (>1 cm) were more common in the PG (computed tomography) and smaller PG (MRI) volume compared with healthy controls. The anatomical and functional abnormalities of PG are not related to the duration of the disease or treatment factors, which may suggest that these are primary features of the disease and are genetically based. This meta-analysis study supports our study.^[11]

These structural changes are of course associated with functional consequences as many studies have shown that serum melatonin and serotonin levels are significantly lower among patients with schizophrenia^[10] this part need more details and many example studies.

Our results strongly suggest that pineal gland has important role in the pathogenesis of schizophrenia. More studies are needed to evaluate the histological and molecular

abnormalities in pineal gland in association of schizophrenia and the possible relation between these changes and the natural history and prognosis of schizophrenia.

CONCLUSION

Our results indicate that patients with schizophrenia have a smaller pineal gland than healthy controls. MRI is an invaluable tool for studying structural brain changes in schizophrenia. This suggests that the pineal gland may play a role in the pathogenesis of schizophrenia.

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